

ADVANCES IN LLM

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Bendamustine: A New Therapeutic Option for Hematologic Malignancies

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H&O What is bendamustine's mechanism of action?

BC Bendamustine (Treanda, Cephalon) was originally developed in East Germany in the 1960s to be a bifunctional molecule with an alkylating agent moiety plus an antimetabolite or purine analog-like component. Although it is clear that bendamustine has alkylating agent-like properties, whether it acts like a purine analog is a subject of controversy. Nevertheless, bendamustine does appear to be noncross-resistant with other alkylating agents *in vitro* and *in vivo*. This agent kills cells by activation of DNA-damage stress responses and apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe. Unlike other alkylating agents, bendamustine activates a base excision DNA repair pathway. However, understanding of its precise mechanism of action is speculative at present.

H&O What are the unmet needs bendamustine is proposed to fill?

BC Bendamustine was shown in studies in East Germany to be active against a variety of malignancies including lymphomas, chronic lymphocytic leukemia (CLL), and a number of solid tumors. Most of the attention in the United States is focused on its use in CLL and non-Hodgkin lymphoma (NHL). There is a need for new agents in patients with CLL, the setting in which the drug was approved for use by the US Food and Drug

Administration (FDA) in March. For example, although the standard regimens for initial treatment (eg, fludarabine and rituximab [Rituxan, Genentech/Biogen Idec] \pm cyclophosphamide) are very effective, they induce substantial adverse effects, particularly immunosuppression and myelosuppression. Some of these regimens are not suitable for elderly patients with CLL, a disease with a median age of presentation in the late 60s to early 70s. Therefore, an agent that is effective but better tolerated is needed. It appears that bendamustine is a well-tolerated drug, even in older patients.

There is also a need for agents that are effective in CLL for patients who have failed frontline therapies such as fludarabine and rituximab with or without cyclophosphamide; chlorambucil; or alemtuzumab (Campath, Bayer), which was recently approved by the FDA. There is not a great deal of information available on bendamustine in the relapsed/refractory setting, and clinical trials are ongoing in this regard.

The only approved agent in patients who have failed fludarabine and rituximab with or without cyclophosphamide is alemtuzumab. This agent was approved initially based on a demonstrated 33% response rate in patients who failed fludarabine and an alkylating agent, prior to the widespread use of rituximab in combination with these frontline drugs. Therefore, it is unknown how effective alemtuzumab is in the typical current practice. Moreover, alemtuzumab is relatively ineffective in the setting of bulky lymph nodes (ie, >5 cm in diameter). In addition, there is no agent approved for use in patients who have received alemtuzumab in the second-line setting and failed. Bendamustine therefore fills a need for patients with relapsed or refractory CLL. This agent's level of efficacy in this context, however, is still being evaluated.

In patients with NHL, there are clearly other unmet needs. In particular, for patients with indolent lympho-

mas, the setting in which most of the data have been generated, frontline regimens for those whose disease requires treatment have included cyclophosphamide, vincristine, and prednisone (CVP) and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and each is currently combined with rituximab (R-CVP and R-CHOP, respectively). Many patients are unable to tolerate regimens such as CHOP because of comorbidities including cardiac problems, and therefore an alternative would be valuable. In preliminary reports from a randomized study by Rummel and associates in Germany, the combination of rituximab and bendamustine was shown to be comparable to R-CHOP with respect to overall and complete response rates, progression-free survival, and overall survival. Importantly, bendamustine-rituximab had a more favorable safety profile. These results are still early, and longer follow-up is needed, but this regimen could provide another therapeutic option for elderly patients or those with comorbidities. This regimen may also be useful for younger patients if the long-term results suggest that it is truly comparable to CHOP, CVP, and CHOP- or CVP-based regimens.

In the relapsed NHL setting, there are few approved agents. Radioimmunotherapy with either iodine-131 tositumomab (Bexxar, GlaxoSmithKline) or yttrium-90 ibritumomab tiuxetan (Zevalin, CTI) is available for relapsed and refractory follicular and low-grade NHLs. However, many patients are not eligible for those treatments, and even if they receive them, other options are needed for subsequent therapy. Here, bendamustine answers another need. Based on data generated first in Germany and confirmed in 2 US trials, response rates of over 70% in rituximab-refractory patients have been demonstrated with bendamustine as a single agent. When combined with rituximab, in the initial study by Rummel and associates, a response rate of over 90% was reported. Indeed, my colleagues and I recently published comparable results from a North American study of this combination, with overall response rates in relapsed indolent and mantle-cell lymphomas of over 90%. These responses can be reasonably durable. Thus, there are several populations of patients for whom there are no other approved therapies, and bendamustine fills their unmet needs.

H&O What were the data that led to bendamustine's initial regulatory approval in CLL?

BC The data that led to the approval by the FDA of bendamustine for the treatment of CLL were based on a direct comparison of bendamustine to chlorambucil, an oral alkylating agent in use for decades for the treatment of this disease. Its use today, however, is much less frequent

than in the past because of the increased efficacy of newer regimens containing fludarabine, particularly those that also include rituximab. Nevertheless, this comparison was conducted in over 300 patients with previously untreated CLL. Using standardized response criteria, the overall response rate was 62% with bendamustine, including 27% complete responses, versus 33% with chlorambucil, including 2% complete responses. With regard to response rate, bendamustine was significantly better. The progression-free survival for patients who received bendamustine was 21.7 months versus 9.3 months for patients who received chlorambucil ($P < .0001$). There was more grade 3/4 neutropenia associated with bendamustine (43% vs 21%), but the rates of treatment-related anemia and thrombocytopenia, as well as gastrointestinal effects, were comparable. The likelihood of infections was comparable, though there were more fevers in patients receiving bendamustine. Therefore, this agent provided greater efficacy with a reasonably favorable toxicity profile. These data led to the approval of bendamustine for CLL in both the frontline and relapsed settings.

H&O What is the ongoing research with bendamustine?

BC There are ongoing studies in Germany comparing fludarabine-based therapy head-to-head with bendamustine-based therapy in patients with follicular lymphoma. It is possible that bendamustine could replace fludarabine in the armamentarium if it turns out to be as effective and less toxic. Not many comparative studies have been initiated because researchers remain at the stage of attempting to incorporate bendamustine into multi-agent regimens. Studies have combined bendamustine with mitoxantrone-based therapies in patients with lymphoma, which did not appear to confer better results than bendamustine alone. The ongoing multicenter VERTICAL trial is combining bendamustine with bortezomib (Velcade, Millennium) and rituximab in the treatment of patients with relapsed and refractory follicular lymphoma. At my institution, a phase I trial is soon to be initiated, which will combine bendamustine with lenalidomide (Revlimid, Celgene) and rituximab for patients with B-cell malignancies. Other bendamustine-based combinations are under development. Once researchers identify very effective and well-tolerated regimens, further comparisons with standard approaches will be conducted.

H&O What questions remain to be answered regarding bendamustine?

BC A number of issues remain to be elucidated regarding this agent. Bendamustine is associated with toxicities

including nausea and vomiting; therefore, prophylactic antiemetics are warranted. This agent can also be associated with myelosuppression, particularly neutropenia and thrombocytopenia, which may be prolonged in patients who have received prior therapies. The degree of associated immunosuppression has not yet been quantified. Whereas bendamustine achieves results in 60% of lymphoma patients who are refractory to alkylating agents, its efficacy in patients who have failed fludarabine is still being evaluated. Furthermore, the optimal dose and schedule are unknown and there are insufficient pharmacokinetic data available on which to base treatment strategies. In phase II trials in rituximab-refractory follicular lymphoma, for example, a dose of 120 mg/m² on days 1 and 2 every 21 days was used. In combination with rituximab, the dose of bendamustine used in lymphoma trials was 90 mg/m². In studies in patients with CLL, the dose used was 100 mg/m² as a single agent and 70 mg/m² in combination with rituximab. The optimal dose as monotherapy and in combination, as well as whether the schedule should be every 3 or 4 weeks, remain to be elucidated. Research is ongoing to attempt to determine the best dose and schedule of administration. My opinion is that the every-3-week schedule is not tolerated as well as the every-4-week schedule, which has comparable efficacy, but we must await evidence from trials.

Suggested Readings

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